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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/737,633	11/15/96	SAMARITANI F	P/42-60

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EXAMINER	
FITZGERALD,D	
ART UNIT	**PAPER NUMBER**
1646	19

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/737,633	Applicant(s) SAMARITANI, et al.
	Examiner David L. FITZGERALD	Group Art Unit 1646

☒ Responsive to communication(s) filed on *16 Apr 1999*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *THREE (3)* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1 and 3-10* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1 and 3-10* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☒ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. The substitute copy of page 1 of the specification, submitted in the amendment filed 16 April 1999, has been entered in the specification and satisfies the requirement therefor (see ¶ 3 of Paper No. 14).

2. Applicant's arguments directed to the Cymbalista ('454) reference in the Brief on Appeal filed 16 April 1999 are persuasive. In particular, the applicability of its teachings regarding the stability of IFN formulations is limited because they relate to lyophilized rather than liquid formulations.

The finality of the last Office action is withdrawn, and the outstanding rejection under 35 U.S.C. § 103 (¶ 4 of Paper No. 14) is withdrawn in favor of new rejections based on a reference which issued after the first Office action in this file. The examiner additionally takes this opportunity to address issues of clarity concerning the claims.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claims 1 and 3-10 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and the claims dependent therefrom are vague and indefinite because it is not clear in the context of the specification what amount of mannitol is considered "stabilizing" or what degree of stability distinguishes the claimed formulations as "stable." Furthermore, as evidenced by Hanisch *et al.*, U.S. Patent No. 5,643,566, discussed below, liquid formulations consisting of IFN-β, HSA, and an aqueous buffer at pH 3.5 were known in the art to be "stable," even in the complete absence of mannitol. The examiner suggests that the claims will be clarified in this regard if "stable" and "a stabilizing amount of" are deleted from claim 1.

The claims are additionally confusing and indefinite as they recite a buffer "capable of maintaining the pH" of the formulation between 3.0 and 4.0; it is not clear whether this actually requires a pH within the recited range. The examiner suggests deletion of the "capable of" construction from claim 1.

Claim 9 is incomplete and indefinite for failing to affirmatively recite the components necessary to realize the preamble recitation of making a formulation of claim 1. The latter claim requires mannitol, a buffer at a pH between 3.0 and 4.0 and, optionally, albumin. Dilution of

IFN-β with "excipients," as that term is employed in the instant disclosure, will not necessarily afford a composition meeting the limitations of claim 1. The replacement of "excipients" with a recitation of the components specified in claim 1 will obviate this ground of rejection.

4. Claims 1, 3, 7, 9, and 10 rejected under 35 U.S.C. § 103(a) as being unpatentable over Hanisch, *et al.* (U.S. Patent No. 5,643,566).

Hanisch describes formulations for the stable storage of "lipophilic proteins," including particularly the exemplified IL-2 and IFN-β. '566 at the abstract. It teaches that a formulation having essentially only IFN-β, human serum albumin, and a buffer (as is obtained following practice of the prescribed purification protocol) may be prepared at an acidic pH, preferably 3.5, and that under such conditions "[t]he β-IFN formulation will remain stable and soluble." '566 at col. 12, lines 53-65. It further teaches that the formulation "can be maintained as a liquid with or without a carbohydrate stabilizer," and that following the optional addition of such stabilizer the formulation may be lyophilized. *Id.* The patent teaches that a number of carbohydrate stabilizers, including mannitol, may be employed in the formulations it describes. '566 at col. 9, lines 21-37. Hanisch does not exemplify a formulation consisting of IFN-β, HSA, a buffer, and mannitol.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare a liquid formulation consisting of IFN-β, HSA, a buffer at pH 3.5, and mannitol, because Hanisch teaches that such formulation will be stable and may be lyophilized, if desired, prior to reconstitution for therapeutic use. It further would have been obvious to dispense the formulation in unit dosage quantities into sterile containers for lyophilization because Hanisch teaches that the "lyophilized formulation can then be reconstituted for clinical administration," and one of ordinary skill in the art would have realized that such use would require sterile containment according to conventional practice in the art. The claimed invention would have been *prima facie* obvious as a whole at the time it was made, especially in the absence of evidence to the contrary.

In traversing the rejection based upon Cymbalista, Hershenson, and Rideout, applicant urges that the prior art teaches that the formulations it describes should be lyophilized (as does Hanisch), whereas the present invention does not require lyophilization. This argument does not establish the patentability of the claimed formulations because the prior art suggests formulations

meeting all of the material and functional limitations of the claims, and it evidences that the stability of such formulations was appreciated. The issue of lyophilization versus storage as a liquid goes to intended use, not any unexpected advantage; it remains that the formulations themselves are directly suggested by the prior art.

5. Claim 5 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Hanisch '566 as applied to claims 1, 3, 7, 9, and 10 above, further in view of Cymbalista *et al.* (U.S. Patent No. 4,647,454).

Cymbalista teaches that acetate buffer at a pH of 3.5 is suitable for making stable formulations of IFN-β. '454 at col. 1, lines 47-56.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare a formulation of IFN-β as described generally by Hanisch '566, employing a pH 3.5 acetate buffer as described by Cymbalista '454, because Cymbalista teaches that IFN-β is stable in acetate buffer at pH 3.5 and that such buffer is suitable for preparing stable pharmaceutical formulations of the IFN. The ordinarily skilled artisan would have realized, in view of the teachings of the references considered collectively, that the acetate buffer described by Cymbalista would be especially suitable for use in the formulations described by Hanisch. The claimed invention would have been *prima facie* obvious as a whole at the time it was made, especially in the absence of evidence to the contrary.

6. Claim 6 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Hanisch '566 as applied to claims 1, 3, 7, 9, and 10 above, further in view of Hershenson *et al.* (U.S. Patent No. 5,004,605).

Hershenson teaches that it is desirable to employ a buffer at a pH between 2 and 4, preferably at a concentration of 10 to 25 mM, to prepare stable formulations of IFN-β. '605 at col. 9, lines 13-20.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare a formulation of IFN-β as described generally by Hanisch '566, employing a buffer at a pH of 2-4 and a concentration of 10 to 25 mM, because Hershenson '605 teaches that IFN-β is stable in an such a buffer and that such buffer is suitable for preparing stable pharmaceutical formulations of the IFN. The ordinarily skilled artisan would have realized, in view of the teachings of the references considered collectively, that 10-25 mM buffers described

by Hershenson '605 would be especially suitable for use in the formulations described by Hanisch. The claimed invention would have been *prima facie* obvious as a whole at the time it was made, especially in the absence of evidence to the contrary.

7. No claim is allowed. However, claims 4 and 8 are patentable over the prior art of record for the following reasons. Hanisch '566 exemplifies unit dosage formulations of IFN-β at 50 MIU/ml immediately prior to lyophilization. See '566 at col. 21, lines 5-24. Because Hanisch teaches that the formulations should be lyophilized, it implicitly teaches away from preparing a formulation having a significantly lower concentration of IFN-β because the artisan would have realized that it is desirable to maintain the lowest possible solution volume to promote the efficiency of lyophilization.

The examiner suggests that entry of the following amendments would render the claims allowable.

> 1. A [~~stable~~] liquid pharmaceutical formulation consisting of <u>from 0.6 to 1 MIU/ml of</u> interferon-beta, [~~a stabilizing amount of~~] mannitol, a buffer <u>at a</u> [~~capable of maintaining the~~] pH [~~of the formulation at a value~~] between 3.0 and 4.0 and, optionally, albumin.
>
> Cancel claim 4.
>
> Change the dependence of claim 5 from claim "4" to claim - 1 - .
>
> 9. <u>A</u> [~~P~~]process for the preparation of a liquid pharmaceutical formulation according to claim 1, comprising [~~the dilution of~~] <u>combining</u> interferon-beta with [~~a solution of excipients~~] <u>mannitol, a buffer at a pH between 3.0 and 4.0 and, optionally, albumin</u>.

8. Any inquiry concerning this communication should be directed to David Fitzgerald, who can be reached by any of the following means:

Telephone	(703) 308-3934
Fax	
All formal papers	(703) 308-4242
Informal communications	(703) 308-0294
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Inquiries of a general nature should be directed to the Technology Center 1 receptionists at (703) 308-0196.

DAVID L. FITZGERALD
PRIMARY EXAMINER
ART UNIT 1646

1 July 1999

The best **time to reach Examiner Fitzgerald** is from 9 a.m. to 4 p.m. (Eastern). If he cannot take a call, a message may be left on his voicemail. Should attempts to reach him be unsuccessful, the acting supervisor for this Art Unit, Paula Hutzell, may be reached at (703) 308-4310.

Most official papers and all informal **communications may be submitted to the PTO by fax.** For specific policies, refer to 37 C.F.R. § 1.6 and the notice published at 1096 O.G. 30. To facilitate their receipt and handling, please —

- Call the examiner when you send an urgent communication.
- **Do not send a duplicate copy** by mail or courier.

Any Internet **e-mail communications will be made of record in the application file**. PTO employees cannot engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. § 122. This policy is more fully set forth in the Interim Internet Usage Policy published in the PTO's *Official Gazette* on 25 February 1997 at 1195 O.G. 89.